

09/868501

JB19 Rec'd/PCT/PTO 18 JUN 2001

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		ATTORNEY'S DOCKET NUMBER CHAIN 4A
TRANMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		U.S. APPLICATION NO (If known, see 37 CFR 1.5) 09/868501
INTERNATIONAL APPLICATION NO. PCT/US99/30066	INTERNATIONAL FILING DATE 17 December 1999	PRIORITY CLAIMED 17 December 1998
TITLE OF INVENTION INCREASING BRAIN GLUCOSE UTILIZATION		
APPLICANT(S) FOR DO/EO/US Daniel CHAIN et al.		
<p>Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information</p> <ol style="list-style-type: none"> 1. <input checked="" type="checkbox"/> This is a FIRST submission of items concerning a filing under 35 U.S.C. 371 2. <input type="checkbox"/> This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371 3. <input checked="" type="checkbox"/> This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1) 4. <input checked="" type="checkbox"/> The US has been elected in a Demand by the expiration of 19 months from the priority date (PCT Article 31). 5. <input checked="" type="checkbox"/> A copy of the International Application as filed (35 U.S.C. 371(c)(2)) <ul style="list-style-type: none"> a. <input type="checkbox"/> is attached hereto (required only if not transmitted by the International Bureau) b. <input checked="" type="checkbox"/> has been communicated by the International Bureau. c. <input type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US). 6. <input type="checkbox"/> An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)) 7. <input checked="" type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)) <ul style="list-style-type: none"> a. <input type="checkbox"/> are transmitted herewith (required only if not transmitted by the International Bureau). b. <input type="checkbox"/> have been communicated by the International Bureau. c. <input type="checkbox"/> have not been made; however, the time limit for making such amendments has NOT expired. d. <input checked="" type="checkbox"/> have not been made and will not be made 8. <input type="checkbox"/> An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)) 9. <input type="checkbox"/> An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)) 10. <input type="checkbox"/> An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)) 		
<p>Items 11. to 16. below concern document(s) or information included:</p> <ol style="list-style-type: none"> 11. <input type="checkbox"/> An Information Disclosure Statement under 37 CFR 1.97 and 1.98 12. <input type="checkbox"/> An Assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included. 13. <input checked="" type="checkbox"/> A FIRST preliminary amendment <ul style="list-style-type: none"> <input type="checkbox"/> A SECOND or SUBSEQUENT preliminary amendment. 14. <input type="checkbox"/> A substitute specification 15. <input type="checkbox"/> A change of power of attorney and/or address letter 16. <input checked="" type="checkbox"/> Other items or information <ul style="list-style-type: none"> <input checked="" type="checkbox"/> Courtesy copy of the International Application as filed. <input checked="" type="checkbox"/> Courtesy copy of the first page of the International Publication (WO 00/35437) <input checked="" type="checkbox"/> Application Data Sheet <input checked="" type="checkbox"/> Courtesy copy of the International Preliminary Examination Report with annexes containing claims 1-30 to be substituted for original claims 1-30 for examination in this case. 		

U.S. APPLICATION NO. (If known, see 37 CFR 1.5)	International Application No PCT/US99/30066	Attorney's Docket No CHAIN 4A
09/868501		

17. [xx] The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492 (a)(1)-(5):

Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO \$1000.00

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO \$860.00

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO \$710.00

International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) \$690.00

International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) \$100.00

CALCULATIONS PTO USE ONLY

ENTER APPROPRIATE BASIC FEE AMOUNT =

\$ 860.00	
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Surcharge of **\$130.00** for furnishing the oath or declaration later than [] 20 [X] 30 months from the earliest claimed priority date (37 CFR 1.492(e)).

\$ 130.00	
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Claims as Originally Presented	Number Filed	Number Extra	Rate
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Total Claims	30 - 20	10	X \$18.00
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Independent Claims	1 - 3		X \$80.00
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Multiple Dependent Claims (if applicable)			+\$270.00
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TOTAL OF ABOVE CALCULATIONS =

\$1,170.00	
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Claims After Post Filing Prel Amend	Number Filed	Number Extra	Rate
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Total Claims	- 20		X \$18.00
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Independent Claims	- 3		X \$78.00
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TOTAL OF ABOVE CALCULATIONS =

\$1,170.00	
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Reduction of $\frac{1}{2}$ for filing by small entity, if applicable Applicant claims small entity status. See 37 CFR 1.27	\$
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SUBTOTAL =

\$1,170.00	
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Processing fee of \$130.00 for furnishing the English translation later than [] 20 [] 30 months from the earliest claimed priority date (37 CFR 1.492(f)).	\$
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TOTAL NATIONAL FEE =

\$1,170.00	
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Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property +	\$
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TOTAL FEES ENCLOSED =

\$1,170.00	
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Amount to be: refunded	\$
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charged	\$
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a. [] A check in the amount of \$ _____ to cover the above fees is enclosed

b. [X] Credit Card Payment Form (PTO-2038), authorizing payment in the amount of \$ 1,170.00, is attached.

c. [] Please charge my Deposit Account No. **02-4035** in the amount of \$ _____ to cover the above fees
A duplicate copy of this sheet is enclosed

d. [XX] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **02-4035**. A duplicate copy of this sheet is enclosed

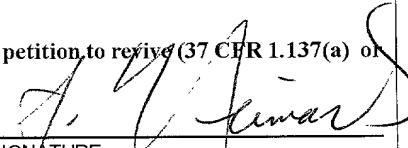
NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO.

**BROWDY AND NEIMARK, P.L.L.C.
624 NINTH STREET, N.W., SUITE 300
WASHINGTON, D.C. 20001
TEL: (202) 628-5197
FAX: (202) 737-3528**

Date of this submission. **Monday, June 18, 2001**

Form PTO-1390 (as slightly revised by Browdy and Neimark)


SIGNATURE
Sheridan Neimark
NAME
20,520
REGISTRATION NUMBER

09/868501

JC18 Rec'd PCT/PTO 18 JUN 2001

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:)	Art Unit:
Daniel CHAIN et al.)	
)	
IA No.: PCT/US99/30066)	
)	Washington, D.C.
IA Filed: 17 December 1999)	
)	
U.S. App. No.:)	
(Not Yet Assigned))	
)	June 18, 2001
National Filing Date:)	
(Not Yet Received))	
)	
For: INCREASING BRAIN...)	Docket No.: CHAIN 4A

PRELIMINARY AMENDMENT

Honorable Commissioner for Patents and Trademarks
Washington, D.C. 20231

Sir:

Contemporaneous with the filing of this case and
prior to calculation of the filing fee, kindly amend as
follows:

IN THE SPECIFICATION

After the title please insert the following
paragraph:

REFERENCE TO RELATED APPLICATIONS

--The present application is the national stage
under 35 U.S.C. 371 of international application
PCT/US99/30066, filed 17 December 1999 which designated the
United States, and which international application was
published under PCT Article 21(2) in the English language.--

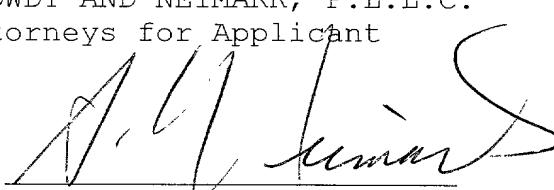
In re of: Daniel CHAIN et al. (CHAIN 4A)

REMARKS

The above amendment to the specification is being made to insert reference to the PCT application of which the present case is a U.S. national stage.

Favorable consideration is earnestly solicited.

Respectfully submitted,
BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant

By: 
Sheridan Neimark
Registration No. 20,520

SN: wrd
Telephone No.: (202) 628-5197
Facsimile No.: (202) 737-3528

USPTO - Patent and Trademark Office

INCREASING BRAIN GLUCOSE UTILIZATIONCROSS-REFERENCE TO RELATED APPLICATIONS

The present application claims priority from provisional applications serial number 60/112,669, filed December 17, 1998, and serial number 60/122,258, filed February 24, 1999, the contents of each of which are hereby incorporated in their entirety.

FIELD OF THE INVENTION

The present invention is directed to a method for improving central insulin sensitivity in the brain for treating senile dementia, Alzheimer's Disease and other dementias, as well as improving mental performance.

BACKGROUND OF THE INVENTION

Glucose is a major energy source for cerebral tissue. Glucose transported to the cerebral tissue is metabolized by hexokinase to glucose-6-phosphate, which is a very important intermediate in the glucose catabolism system. After this, the glucose-6-phosphate enters a metabolic pathway where it is catabolized in order to generate high-energy phosphate compounds, such as ATP, through its linked phosphorylation reaction.

There is a strong linkage between brain glucose utilization and mental performance as illustrated by the use of PET scans as an aid to identifying brain injury and in evaluating new therapies for senile dementia. It has generally been believed that brain glucose utilization is not affected by changes in circulating insulin concentration and changes in the normal diet or eating pattern. It has been argued that a function critical to maintaining life cannot be dependent upon such things as the nature and timing of meals. Indeed, measurements of whole brain glucose utilization do not show any significant overall differences in relation to diet, insulin treatment or diabetes. The ability to measure brain glucose utilization was originally developed by Sokolov and colleagues, cf. Dienel et al (1992). The principle was developed for animal studies and used radiolabelled 2-deoxyglucose, which is taken up by cells through the glucose

transport system, is converted to 2-deoxyglucose-6-phosphate, but cannot be further metabolized. Further, the glucose-6-phosphate only minimally accumulates in the brain. Thus, measurement of trapped 2-deoxyglucose-6-phosphate can be used as an index of brain glucose utilization. In animals, this involves direct extraction of tissues. In humans, 18-fluoro-2-deoxyglucose is used, and this can be detected by PET scanning.

These techniques have been used in both animals and humans to demonstrate that the rate of glucose utilization is not uniform throughout the brain. Furthermore, certain portions and cell types, such as astrocytes, are clearly insulin sensitive (Clarke et al, 1984). Astrocytes are important communicating cells, and the insulin sensitivity of these cells can be demonstrated by *in vitro* studies (Clarke et al, 1984). Diabetes severely affects glucose utilization by astrocytes, and it has also been shown that astrocytes can develop insulin resistance.

In vivo studies in rats have shown that glucose utilization is reduced 50% by anesthetic, and that overall glucose utilization by insulin-resistant fa/fa rats is less than in lean littermates. Corticosterone decreased glucose utilization in the limbic regions, but increased utilization in thalamic regions. Adrenalectomy increased glucose utilization in limbic regions. Minipump infusion of insulin for four days to create hyperinsulinaemia reduced glucose utilization in the suprachiasmatic nucleus (affecting circadian rhythm), locus coeruleus and basolateral amygdala. All of these studies indicate that glucose utilization in discrete areas of the brain is under complex control and can be modified by circulating hormones and possibly by nutrients (Doyle et al, 1995).

The development of memory loss and dementia is generally an age-related process. It is well known that insulin-stimulated fuel utilization in peripheral tissues, such as skeletal muscle, often declines with age and insulin resistance develops. The nature of the insulin resistance is generally related to a reduced amplification of the insulin

signaling process, so that insulin is less efficient in activating the normal insulin response. Glucose utilization in the brain also decreases with age (Smith and Sokoloff in The Aging Brain). This might suggest that insulin resistance in discrete brain areas and cell types may play a role in central glucose utilization, resulting in reduced mental performance. On the other hand, as glucose utilization in the brain is believed to be under complex control, one cannot predict whether or not insulin resistance plays a major role in age- decreased brain glucose utilization.

A number of therapies have been developed to inhibit memory loss and dementia in aging patients. However, none of these therapies depends upon controlling insulin action in the brain.

Duelli et al (1994) disclose that a decrease in cerebral glucose utilization may correspond to changes in morphobiological parameters which have been found in patients with Alzheimer's Disease. However, there is no indication that any type of treatment of this decrease in cerebral glucose utilization could be used to prevent or treat Alzheimer's Disease.

Blum-Degen et al (1995) disclose that there is a measurable decrease of *in vivo* and post-mortem cerebral glucose metabolism, and that insulin plays an important role in regulating brain glucose homeostasis in the central nervous system. It has been suggested that the reduction of brain glucose metabolism in neuro-degenerative disorders may be related to a defect of the neuronal insulin-insulin receptor interaction. However, there is no specific disclosure of treating neuro-degenerative disorders with substances which improve insulin sensitivity.

Hoyer et al (1996) disclose that intracerebroventricularly-administered insulin exerts anabolic effects on cerebral glucose/energy metabolism. However, there is no indication that administering a substance to improved insulin sensitivity could be useful in treating age-related brain disorders, such as dementia.

Dore et al, (1997) disclose that insulin receptor sites are not markedly altered during the normal aging process in the Long Evans rat, despite significant learning deficits in memory-impaired aged animals. This suggests that insulin action in the brain does not contribute to the age-related memory loss.

Cullingford (1998) reported that PPAR (peroxisome proliferator-activated receptor) gamma mRNA was expressed at a similar level to PPAR alpha mRNA in adult rat astrocytes, but there is no indication that this receptor might be involved with regulating insulin action and glucose metabolism in this cell type.

Granneman et al (1998) show that PPAR is strongly expressed in immature oligodendrocytes, suggesting a role in oligodendrocyte differentiation. One thiazolidinedione compound, Pfizer CP68722, increased the number of oligodendrocytes in glial cultures. However, there is no indication of a connection between this work and improved central glucose utilization.

Romeo et al, in U.S. Patent 5,556,843, disclose that phosphoryl-L-serine-N-acyl-sphingosine can increase glycemia and histamine levels, resulting in cerebral glucose accumulation. This compound can be used in therapies associated with a slowdown of cerebral metabolism, in involutive cerebral syndromes of different origins, and Alzheimer's Disease, memory loss, senile dementia, etc. Phosphoryl-L-serine-N-acyl-sphingosine is said to be useful in treating insulin-dependent diabetes. However, there is no indication that any other drug used for treating diabetes could be used to treat senile dementia or other types of neurological conditions. In fact, phosphoryl-L-serine-N-acyl-sphingosine has no connection to insulin action or insulin resistance.

Ohmoto et al, in U.S. Patent 5,710,153, disclose tetrazole compounds which are used in treating, among other conditions, insulin-dependent diabetes and neural diseases, such as Alzheimer's Disease and Parkinson's Disease. This treatment depends on inhibition of ICE enzymatic activation

which leads to prevention of conversion of pre-IL-1 β to IL-1 β and presumably relates to preventing the inflammatory action of IL-1 β . Thus, these compounds have no correlation to insulin action or insulin resistance.

5 Guthikonda et al, in U.S. Patent 5,629,322 disclose cyclic amidine analogs as inhibitors of nitric oxide synthase which can be used to treat Type I diabetes and dementia. However, there is no indication that there is any effect on glucose metabolism directly from these compounds. In fact, the inhibitors of nitric oxide synthase are associated with inflammatory reactions in insulin-dependent diabetes rather than glucose utilization.

10 Shapiro, in U.S. Patent 5,668,117, discloses treating neurological diseases, such as diabetic neuropathy, with at least one carbonyl trapping agent, alone or in combination with a therapeutically effective co-agent. However, there is no indication that the carbonyl trapping agent acts by increasing glucose metabolism. The carbonyl trapping agents can be used with insulin derivatives and other conventional 0 medicaments for treating diabetes.

15 Torii et al, in U.S. Patent 5,693,614, disclose the use of α -FGF for treating senile dementia of the ischemic and hypoglycemic types, stating that the failure of energy metabolism in the brain resulting from hypoglycemia elicits this type of lesion formation. However, α -FGF is not related to any insulin- stimulated process, and there is no indication that this is a conventional treatment for diabetes which can then be used to treat hypoglycemic dementia.

20 Nakagama et al (1996) disclose that TAK-147, a novel acetylcholinesterase inhibitor when given daily for 40 days to aged rats, increased energy metabolism and increased brain glucose utilization. However, there is no indication that this compound has any effect whatsoever on insulin sensitivity, nor does it act at the PPAR gamma receptor.

25 Jannetta, in U.S. Patent No. 5,962,004, discloses neurogenic diabetes mellitus can be treated by relieving pressure from a region of the brainstem within the cranium of a patient with a neuroendocrine servomechanism. By relieving

pressure on the neuroendocrine servomechanism, the disease is ameliorated. However, this has nothing to do with increasing brain function.

5 Kumagai, in *Diabetes Metab. Res. Rev.* 15(4):261-273, Jul-Aug, 1999, discloses that neural tissue is entirely dependent on glucose for normal metabolic activity, and that metabolism in the brain is dependent upon adequate glucose delivery from the systemic circulation. Changes in endothelial glucose transport may have profound consequences on glucose delivery to these tissues and major implications in the development of two major diabetic complications, namely, insulin-induced hypoglycemia and diabetic retinopathy.

10 Hasselbalch et al., in *Diabetes* 48:(10): 1915-1921, October, 1999, disclose that hyperinsulinaemia within the 15 normal physiologic range does not affect blood brain barrier glucose transport or net cerebral glucose metabolism. However, there is nothing in this article that deals with 20 increasing brain glucose metabolism.

25 Another problem associated with treating dementia by increasing brain glucose metabolism is that for patients with 30 normal serum glucose it is important to treat only brain glucose metabolism. Accordingly, it is important to deliver 35 agents for treating brain glucose metabolism to the cerebral tissue. Unfortunately, the blood brain barrier is the major 40 obstacle for delivering most medication to the central nervous system. The capillaries in the brain parenchyma possess high-resistance, tight junctions between the endothelial cells. The cells also lack pores, so that the brain capillary 45 endothelium behaves like a continuous lipid bilayer. Diffusion through this bilayer, the physical blood brain 50 barrier, is largely dependent on the lipid solubility of the solute. Water-soluble molecules (such as glucose, essential 55 amino acids, glutamate) enter the brain almost exclusively by carrier-mediated transport.

60 Various strategies have been applied to direct medications specific for the central nervous system into the brain. An invasive procedure that includes surgical implantation of an intraventricular catheter followed by

pharmaceutical infusion into the ventricular compartment
delivers a metabolically unstable compound only to the surface
of the brain, cf. Poplack et al (1981). Transient opening of
the tight junctions of the intracarotid infusion of an
osmotically active substance (e.g., mannitol, arabinose) in
high concentrations (>1M) may facilitate an indiscriminate
delivery of molecules that otherwise cannot cross the blood
brain barrier, as shown in Neuwelt et al (1984). However,
this procedure is accompanied by severe toxic effects which
can lead to inflammation, encephalitis, and seizures. These
invasive procedures are only justified for some life-
threatening conditions and are not acceptable for less serious
illness.

A non-invasive method for peptide delivery into the
central nervous system has been suggested that uses the
formation of chimeric peptides, cf. Pardridge (1986). This
strategy relies on the presence of specific receptor-mediated
transcytosis systems in the blood brain barrier for certain
larger peptides, such as insulin, insulin-like growth factor,
transferrin, and albumin. Covalently coupling (e.g., via
disulfide bonds) a non-transportable peptide to these
transport vectors results in a chimeric peptide that can also
undergo receptor-mediated transcytosis, and the active peptide
can be released by its enzymatic cleavage in the central
nervous system. However, these carriers are not brain-
specific, as uptake by non-neural cells or cells outside the
central nervous system has been shown. Low amounts of the
peptide relative to the carrier molecule, as well as the
receptor-based cellular transport mechanism that has
physiologically limited transporter capacity (saturable) also
prevent pharmacologically significant amounts from entering
the brain. Finally, release of the active peptide from the
conjugate has not been documented.

Another method for peptide delivery is a simple
pharmacologically based approach in which peptide "prodrugs"
are administered that are lipophilic esters or amides of the
molecule (Tsuzuki et al, 1991). Although the acquired
lipophilicity of these prodrugs may assure penetration of the

blood brain barrier, as well as other membranes, this is not the sole factor involved in the transport of a peptide into the central nervous system. Blood brain barrier transport of cyclosporin, which is one of the most lipid soluble peptides, is paradoxically low because of peptide degradation, cf. Beagley et al, 1990).

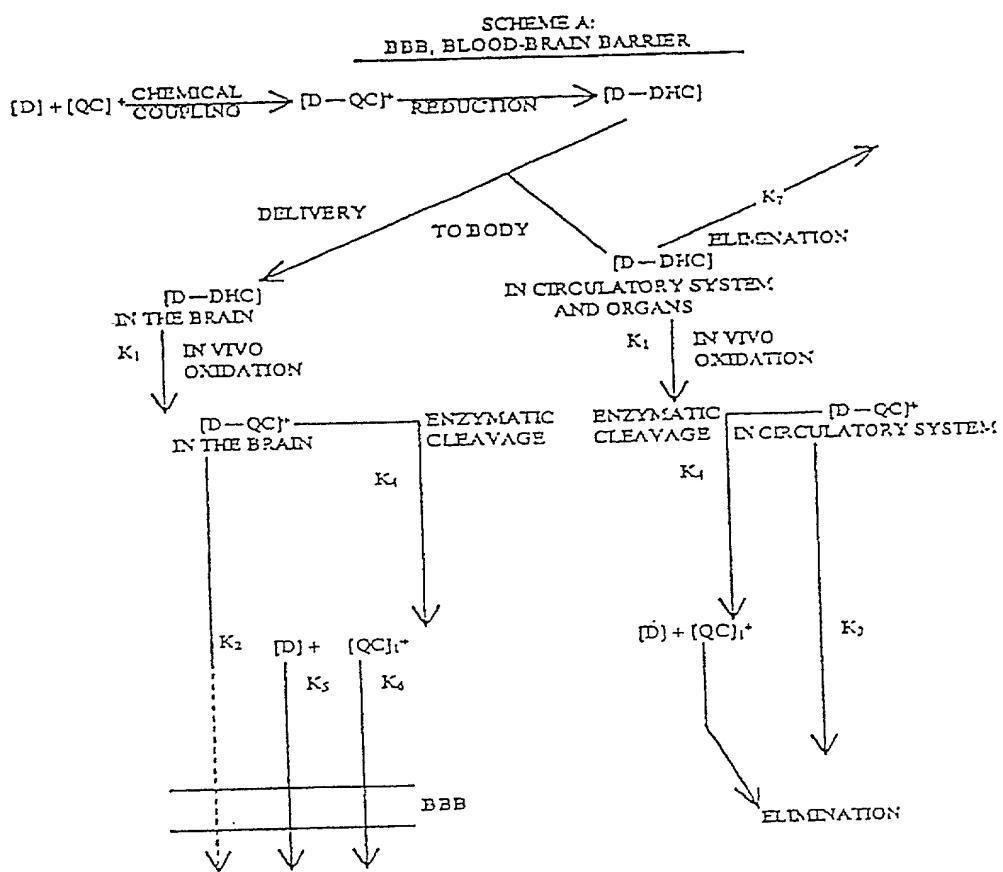
A dihydropyridine-pyridinium redox system has recently been successfully applied to delivery to the brain of a number of drugs. Generally speaking, according to this system, a dihydropyridine derivative of a biologically active compound is synthesized, which derivative can enter the central nervous system through the blood-brain barrier following its systemic administration. Subsequent oxidation of the dihydropyridine species to the corresponding pyridinium salt leads to delivery of the drug to the brain.

Four main approaches have been used thus far for delivering drugs to the brain using a redox system. The first approach involves derivation of selected drugs which contain a pyridinium nucleus as an integral structural component. This approach was first applied to delivering to the brain 2-methylpyridinium-2-carbaldoxime chloride (2-PAM), the active nucleus of which constitutes a quaternary pyridinium salt, by way of the dihydropyridine latent-initiated prodrug form thereof. Thus, a hydrophilic compound (2-PAM) was made lipoidal by making its dihydropyridine form (Pro-2-PAM) to enable its penetration through lipoidal barriers. This simple prodrug approach allowed the compound to get into the brain, as well as into other organs. However, this manipulation did not and could not result in any brain specificity. On the contrary, such approach was limited to relatively small molecule quaternary pyridinium ring-containing drug species, and did not provide the overall ideal result of brain-specific, sustained release of the desired drug, with concomitant rapid elimination from the general circulation, enhanced drug efficacy and decreased toxicity. There was no "trapping" in the brain of the 2-PAM formed *in situ*, and consequently there was no sustained delivery of the 2-PAM. The 2-PAM was eliminated as quickly from the brain as from

the general circulation and other organs, cf. U.S. Patents 3,929,813 and 3,962,447, and 5,624,894, which are hereby incorporated by reference in their entireties, including all references cited therein.

5 Subsequent extension of this approach to delivering a much larger quaternary salt, berberine, to the brain via its dihydropyridine prodrug form was, however, found to provide site-specific, sustained delivery to the brain of that anticancer agent, cf. Bodor et al (1981). However, this
10 approach is limited to delivery of active quaternary pyridinium salts.

A second approach for delivering drugs to the brain using a redox system involves the use of a dihydropyridine/pyridinium carrier chemically linked to a biologically active compound. Bodor et al (1981) outlines a scheme for this specific and sustained delivery of drug species to the brain, as depicted in the following Scheme A:



According to the scheme, a drug [D] is coupled to a quaternary carrier [QC]⁺ and the resulting [D-QC]⁺ is then chemically reduced to the lipoidal dihydro form [D-DHC]. After administration of [D-DHC] *in vivo*, it is rapidly distributed throughout the body, including the brain. The dihydro form [D-DHC] is then *in situ* oxidized (rate constant k₁) by the NAD-NADH system to the ideally inactive original [D-QC]⁺ quaternary salt which, because of its ionic hydrophilic character, should be rapidly eliminated from the general circulation of the body, while the blood-brain barrier should prevent its elimination from the brain (K₃>>K₂; K₃>>K₁).

Enzymatic cleavage of the [D-QC]⁺ that is "locked" in the brain effects a sustained delivery of the drug species [D], followed by its normal elimination (K₅), metabolism. A properly selected carrier [QC]⁺ will also be rapidly eliminated from the brain (K₆>>K₂). Because of the facile elimination of [D-QC]⁺ from the general circulation, only minor amounts of drug are released in the body (K₃>>K₄); [D] will be released primarily in the brain (K₄>K₂). The overall result ideally is a brain-specific sustained release of the target drug species.

Specifically, Bodor et al worked with phenylethylamine as the drug model. That compound was coupled to nicotinic acid, then quaternized to give compounds that were subsequently reduced by sodium dithionite. Testing of the N-methyl derivative *in vivo* supported the criteria set forth in Scheme A. Bodor et al speculated that various types of drugs might possibly be delivered using such carrier systems and indicated that use of N-methylnicotinic acid esters and amides and their pyridine ring-substituted derivatives was being studied for delivery of amino- or hydroxyl-containing drugs, including small peptides, to the brain. No other possible specific carriers were disclosed. Other reports of this work with the redox carrier system have appeared, particularly as disclosed in U.S. Patent 4,430,601 and Bodor et al (1983) and Bodor U.S. Patent 4,540,564.

Bodor '564, which patent is hereby incorporated by reference in its entirety, specifically discloses applying the dihydropyridine-pyridinium salt carrier system to amino acids

and peptides, particularly small peptides having 2 to 20 amino acid units. Thus, in the carrier system applied to amino acids and peptides, the free carboxy function is protected in an effort to prevent premature metabolism, e.g., with an ethyl ester, while the trigoneline-type carrier is linked to the amino acid or peptide through its free amino function.

Oxidation of the dihydropyridine carrier moiety *in vivo* to the 5 ionic pyridinium salt carrier/drug entity prevents elimination thereof from the brain, while elimination from the general 10 circulation is accelerated. Subsequent cleavage of the quaternary carrier/drug species results in sustained delivery 15 of the amino acid or peptide (e.g., tryptophan, GABA, leu-enkaphalin, etc.) to the brain and facile elimination of the carrier moiety. This method is quite useful for delivery of 20 amino acids. In the case of peptides, however, the typical suggested carboxy protecting groups do not confer sufficient 25 lipophilicity to the peptide molecule. Moreover, this 30 approach neither addresses the problem of the enzymatic blood-brain barrier nor suggests a means of avoiding that problem.

The third approach for delivering drugs to the brain 35 using a redox system provides derivatives of centrally acting 40 amines in which a primary, secondary or tertiary amino 45 function has been replaced with a dihydropyridine/pyridinium 50 salt redox system. These brain-specific analogs of centrally 55 acting amines have been described in U.S. Patents 4,771,059, 60 5,082,853 and 5,296,483, all of which are hereby incorporated 65 by reference in their entirety. The dihydropyridine analogs 70 act as a delivery system for the corresponding biologically 75 active quaternary compounds *in vivo*. Due to its lipophilic 80 nature, the dihydropyridine analog will distribute throughout 85 the body and has easy access to the brain through the blood 90 brain barrier. Oxidation *in vivo* then provides the quaternary 95 form, which is preferentially "locked" in the brain. In contradistinction to the drug-carrier entities described in 100 Bodor '564 and related publications, however, there is no readily metabolically cleavable bond between drug and 105 quaternary portions, and the active species delivered is not

the original drug from which the dihydro analog was derived, but rather is the quaternary analog itself.

In the analog systems described in Bodor U.S. Patents 5,082,853, 4,771,059; and 5,296,483, as applied to amino acids and peptides, the free carboxyl function is, thus, protected to prevent premature metabolism while the dihydropyridine-pyridinium salt type redox system replaces the free amino function in the amino acid or peptide.

As described in the above Bodor patents, the chemical processes for preparing the redox analog derivative replace any free amino function in the selected drug with the redox analog system. When these processes are applied to amino acids, they provide a redox amino acid which no longer contains a free amino function for linkage to another amino acid or peptide via a peptide bond (-CONH-). Such an analog amino acid can, thus, only be used to prepare a peptide having the analog amino acid located at the peptide's N-terminus. This limits use of the redox analog amino acids in peptide synthesis. Moreover, this approach is not designed to deliver the original peptide to the brain, since there is no cleavable bond between peptide and quaternary portions. Rather, the redox portion in this approach becomes an inherent, essentially inseparable, part of a new peptide analog. Furthermore, this approach does not address the problem of the enzymatic blood-brain barrier or suggest a means for avoiding the premature degradation caused by the highly active neuropeptide degrading enzymes.

The fourth redox approach is designed to provide redox amino acids which can be used to synthesize peptides having a redox analog system inserted at a variety of locations in the peptide chain, including non-terminal positions, and has been described in Bodor U.S. Patent 4,888,427. These amino acids contain a redox system appended directly or via an alkylene bridge to the carbon adjacent to the carboxyl carbon.

However, this fourth redox approach, like the third approach discussed above, is not designed ultimately to deliver the original peptide to the brain because there is no cleavable bond between the peptide and the quaternary

portions. Again, the redox system becomes an integral part of a new peptide analog, not a means for ultimately delivering the original peptide to the brain. Moreover, this approach also does not address the problem of the enzymatic blood brain barrier or suggest a means for avoiding deactivation of the peptide by enzymes before it achieves its therapeutic objectives.

SUMMARY OF THE INVENTION

It is an object of the present invention to overcome the aforementioned deficiencies in the prior art.

It is another object of the present invention to increase brain glucose utilization in circumstances where brain glucose utilization is sub-optimal for normal mental performance by increasing insulin sensitivity of insulin-sensitive cells in the brain.

It is a further object of the present invention to prevent and treat age-related memory loss and dementia.

It is another object of the present invention to act on the nuclear receptors PPAR gamma, PPAR delta, and PPAR alpha to prevent or reduce age-related memory loss and dementia.

It is still another object of the present invention to provide a method for delivering drugs which increase brain glucose utilization directly to the central nervous system.

It is another object of the present invention to provide drugs which increase brain glucose utilization in the central nervous system in the form of prodrugs.

According to the present invention, brain glucose utilization can be increased by administering an agent that improves central nervous system insulin sensitivity. By improving insulin sensitivity in the central nervous system, brain glucose utilization is improved and age-related memory loss and dementia can be prevented and/or reduced. More specifically, compounds that interact with the PPAR gamma PPAR delta and PPAR alpha receptors, such as thiazolidinedione and other agents that improve insulin sensitivity, are used to treat senile dementia, Alzheimer's Disease and other dementias, as well as to improve mental performance. These

compounds are known to improve insulin sensitivity of peripheral tissues in non-insulin-dependent diabetic patients and are useful in treating non-insulin-dependent diabetes. It has now, surprisingly, been found that the same compounds improve glucose utilization in the central nervous system, leading to improved mental performance, particularly in patients who are otherwise not sensitive to insulin.

More specifically, the present invention provides, in one embodiment, administering certain known thiazolidinedione compounds and derivatives thereof and/or non-thiazolidinedione insulin sensitizers/anti-hyperglycemic agents and derivatives thereof, to an individual who is neither in a state of non-insulin-dependent diabetes (NIDD) nor in a state of general impaired glucose tolerance, but who has symptoms of reduced mental performance. Any pharmaceutical useful in improving insulin sensitivity in non-insulin dependent diabetes patients would be expected to be useful in improving the mental capacity of patients who are neither in a state of NIDD or in a state of general impaired glucose performance.

A number of compounds for the treatment of NIDD have been developed or are under development. These compounds include thiazolidinediones, including troglitazone (Sankyo, Warner-Lambert/Parke Davis, Glaxo), rosiglitazone (Smith Kline Beecham) and pioglitazone (Takeda, Lilly). Other useful compounds include oxazolidinediones, such as JTT 501 (Japan Tobacco), and non-chiral acyclic agents, such as GW 262570 (Glaxo Wellcome). All of these agents act on the nuclear receptor PPAR gamma. According to the present invention, these compounds may also be used to improve central nervous system insulin sensitivity in non-NIDD patients who have symptoms of reduced mental performance. Willson et al., in WO 97/31907 describe substituted 4-hydroxy-phenylalcanoic acid derivatives with agonist activity to PPAR gamma which can be used to improve central nervous system insulin sensitivity in NON-IDD patients in need thereof. The entire contents of this patent are hereby incorporated.

It is believed that activation of PPAR gamma receptors is the basis of the metabolic action. PPAR gamma receptors form

heterodimers with RxR receptors and the heterodimers interact with PPAR response elements to regulate transcription. Thus, activators for the RxR receptors are also insulin sensitizers (Mukherjie et al, 1997).

5 Petrova et al., in *Proc. Natl. Acad. Sci. USA* 96(8):4668-
73, April 13, 1999, and Kitamura et al., *Nuerosci. Lett.*
10 262(2):129-32, March 5, 1999, note that the peroxisome
proliferator-activated receptor-gamma (PPAR-gamma) in glial
cells is activated by anti-diabetic thazolidinediones as well
as by natural ligands. Kitamura et al. in *Biochem. Biophys.*
15 *Res. Comm* 1999 January 27, 254(3):582-6, found that in brains
of patients with Alzheimer's disease, PPAR gamma level was
increased in the cytosolic fraction but not in the
particulatefraction. These results suggest that PPAR gamma
activators have inhibitory effects on inflammatory events in
the brains of patients with Alzheimer's disease.

DETAILED DESCRIPTION OF THE INVENTION

20 Brain glucose utilization is improved, either in the
entire brain, or in discrete areas or in specific cell types,
by administering an agent that improves insulin sensitivity in
the brain. Specific types of cells affected include
25 astrocytes, which are major communicating cells, glial cells
and cells in the blood brain barrier. Specific areas of the
brain affected which affect memory loss and dementia are the
blood brain barrier microvessels and/or the areas of the brain
associated with mental performance or memory.

30 Of particular importance in improving brain glucose
utilization are thiazolidinediones, such as troglitazone,
rosiglitazone, pioglitazone, darglitazone and englitazone and
derivatives thereof. Other types of agents that have been
found to improve brain glucose utilization are
35 oxazolidinediones, such as JTT 501, and non-chiral acyclic
agents, such as GW 262570, as well as substituted 4-hydroxy-
phenylalcanoic acid derivatives with agonist activity to PPAR

gamma. More specific types of compounds which improve brain glucose utilization are compounds which activate the PPAR gamma receptor, or where the agent has agonist or partial agonist activity at the PPAR gamma receptor.

5 Among the thiazolidinedione compounds which have been found to improve brain glucose utilization are those described in Olefsky et al, U.S. Patents 5,478,852 and 5,708,012, the entire contents of each of which are hereby incorporated in their entirety, including all references cited therein.
10 Additional such thiazolidinedione derivatives are disclosed in Antonucci et al, U.S. Patents 5,457,109 and 5,602,133, the entire contents of which are hereby incorporated by reference, including all references cited therein.

15 Substituted thiazolidinedione derivatives, such as those disclosed in Hindley et al U.S. Patents 5,464,169 and 5,756,525, and in Cantello et al (1994), are also expected to be useful in improving brain glucose utilization and, thus, mental performance in patients in need thereof. The entire contents of each of these are also hereby incorporated by reference, including all references cited therein.

20 Non-thiazolidinedione insulin sensitizing agents, such as those disclosed by Buckle et al (1996a and 1996b) and substituted 4-hydroxy-phenylalcanoic acid derivatives, such as those described in Willson et al. patent number WO 9731907, the entire contents of each of which are hereby incorporated by reference in their entirety, including all references cited therein, are also expected to improve brain glucose utilization, and, thus, mental performance in patients in need thereof.

25 Hypoglycemic alkaloids, such as quindoline and cryptolepine, which may be obtained from extracts from *Cryptolepsis sp.*, as disclosed in Luo et al U.S. Patent 5,629,319, as well as triterpenoid substances, such as those disclosed in Inman et al U.S. Patent 5,691,386, and eremophilanolide sesquiterpenes, such as described in Inman et al U.S. Patent 5,747,527, the entire contents of each of which being hereby incorporated by reference in their entirety,

including all references cited therein, can also be used to treat or prevent dementia and memory loss in accordance with the present invention.

Other compounds for improving insulin sensitivity are disclosed in Vyas et al U.S. Patent 5,700,820; Ubillas et al U.S. Patent 5,674,900; and Dominianni et al U.S. Patent 5,641,796, the entire contents of each of which is hereby incorporated by reference in their entirety, including all references cited therein. These compounds include polymorphic forms of troglitazone, terpenoid-type quinones and C-substituted pentacycloazoles and N-alkyl substituted pentacycloazoles.

Other types of agents which improve brain glucose utilization for improving insulin sensitivity are those which selectively activate one of the sub-types of the human PPAR gamma receptor, namely PPAR gamma 1 and PPAR gamma 2, or where the agent activates a RxR receptor that forms a heterodimer with a PPAR gamma receptor, for example, ligand 100268, which is an RxR receptor ligand.

In addition to the compounds enumerated above, the agent can be a natural product, such as extract of *Cryptolepsis* or derived from a natural product such as cryptoleptine.

More specifically, compounds which activate the PPAR gamma receptor or which have agonist activity at the PPAR gamma receptor are useful in improving insulin sensitivity, thereby improving central glucose utilization and ameliorating the memory loss and dementia associated with Alzheimer's Disease and various other types of dementia. Additional types of compounds which are useful include those which activate the PPAR delta receptor or the PPAR alpha receptor.

For purposes of the present invention, "derivative" of the compounds enumerated means chemical modifications of the active compounds which substantially retain the desired activity of the compounds, i.e., the activity of improving central nervous system insulin sensitivity and increasing brain glucose utilization.

Strategies have been specifically tailored to achieving delivery of an agent directly to the central nervous system, i.e., to crossing the blood brain barrier, based upon "sequential metabolism" of a prodrug (cf. Bodor et al, 1992; 5 Prokai et al, 1994; Bodor et al, 19??). In one embodiment of a prodrug form of an agent according to the present invention, the modifying group comprises an alkyl ester to facilitate blood-brain barrier permeability.

In one embodiment of the present invention, the compounds 10 for activation of PPAR gamma receptors or which have agonist activity at the PPAR gamma receptor are delivered across the blood brain barrier by packaging the compounds in a molecular environment which disguises the nature of the compound. This 15 environment provides a biolabile, lipophilic function to penetrate the blood brain barrier by passive transport.

In another embodiment of the present invention, the pharmacologically active molecule provides a dihydropyridine-type redox moiety for targeting the compound to the brain and providing "lock-in" as the pyridinium salt. A spacer is 20 placed between the redox moiety and compound designed to enhance the sequential metabolism of the "molecularly packaged" compound. The spacer may be an amino acid or di- or tri-peptide spacer, or any other short group that is 25 compatible with the compound to be administered and that can readily be cleaved *in vivo* to release the active compound.

In another embodiment of the present invention, a cell scattering factor, hereinafter denoted "egressin", isolated from a clone derived from a human metatstaic melanoma (M3827), as described in Wier et al U.S. Patent 5,039,794, the entire 30 contents of which are hereby incorporated by reference, is used to aid in transporting drugs across the blood brain barrier to increase glucose metabolism in the central nervous system. Egressin disperses endothelial cells and acts on the cell-cell junctions of the endothelial cells lining the blood 35 vessels. The dissociation of these junctions increases the permeability of the vessels and decreases the effectiveness of

the blood brain barrier. Thus, egressin aids in transporting drugs for improving glucose utilization across the blood brain barrier for treating the central nervous system.

In this embodiment, an amount of egressin effective for
5 the dissociation of the cell-cell junction of endothelial cells is administered intravenously along with a therapeutically effective compound for improving glucose utilization in the brain.

Another method for enabling the compounds used in the
10 present invention to cross the blood brain barrier is to formulate the compounds such that the compounds are non-ionic when they reach the blood stream and would be subsequently enzymatically oxidized to release the compound in a

therapeutic amount at the brain. These prodrugs include
15 compounds which contain a tertiary nitrogen atom exhibiting a low basicity, i.e., a pKa below 7.4. On this basis, the skilled artisan can readily appreciate that such compounds, when introduced into the bloodstream of a warm-blooded animal whose pH is about 7.4, would remain essentially non-ionic,
20 thus permitting the prodrug form to be highly protein bounded and/or enter the erythrocytes and, thus, to pass through the blood brain barrier and be subsequently enzymatically oxidized to release the active compound in high bioavailability at the
brain.

Where appropriate, the compounds can be provided in the acid addition salt form for the sole purpose of rendering stability to the prodrug free base form prior to administration. Once the prodrug compounds are administered by any route, the salt moiety is "cleaved", thus releasing the remaining tertiary amine form, which readily transcends the blood brain barrier. Next, the prodrug can be enzymatically oxidized to the active compound in an analogous manner to the nicotinamide dinucleotide co-enzyme mediated oxido-reduction system, wherein the coenzyme, in turn, is reduced to the dihydro form (NADH). For purposes of the present invention, the term "prodrug" refers to a derivatized form of a proven drug which, when administered to an individual, is

enzymatically or otherwise acted upon in the bloodstream to release the drug at the therapeutic site or sites of activity. In the present invention, the therapeutic site is the central nervous system.

The compounds used to increase glucose utilization in the brain can be provided in the form of prodrugs to alter the biodistribution of the compounds, e.g., to allow compounds which would not typically cross the blood-brain barrier to cross the blood-brain barrier. For example, an anionic group, e.g., a sulfate or sulfonate, can be esterified, e.g., with a methyl group or a phenyl group to yield a sulfate or sulfonate ester. When the sulfate or sulfonate ester is administered to a subject, the ester is cleaved, enzymatically or non-enzymatically, reductively or hydrolytically, to reveal the anionic group. Such an ester can be cyclic, e.g., a cyclic sulfate of sultone, or two or more anionic moieties may be esterified through a linking group.

An anionic group can be esterified with moieties (e.g., acyloxymethyl esters) which are cleaved to reveal an intermediate compound which subsequently decomposes to yield the active compound. In another embodiment, the prodrug is a reduced form of a sulfate or sulfonate, e.g., a thiol, which is oxidized *in vivo* to the therapeutic compound. Furthermore, an anionic moiety can be esterified to a group which is actively transported *in vivo*, or which is selectively taken up by target organs. The ester can be selected to allow specific targeting of the therapeutic moieties to the brain.

Carrier molecules may also be used to transport the active compounds to the brain. The carrier molecule may include a moiety capable of targeting the therapeutic compound to the brain by either active or passive transport. Illustratively, the carrier molecule may include a redox moiety. Many targeting moieties are known, including those disclosed in patents to Bodor 4,540,564, 5,389,623, and 5,525,727, the entire contents of which are hereby incorporated by reference, as well as asialoglycoproteins, such as those disclosed in Wu et al U.S. Patent 5,166,320.

Other carrying moieties include ligands which are transported into cells via receptor-mediated endocytosis.

Other means for carrying a prodrug or an active agent across the blood-brain barrier involve coupling either a 5 prodrug or an active agent to a carrier. These carriers include fatty acids, inositol, 1,4-dihydropyridine, lipids, proteins, and peptides. The proteins and peptides can be synthetic or naturally occurring. The term peptide is intended to include small proteins and particularly those 10 molecules having on the order of about 100 amino acids or fewer. Examples of proteins useful as carriers include antibodies specific for receptors within the brain, albumin, insulin, drugs, or growth factors.

Fatty acid carriers preferably have between about 16 and 15 26 carbon atoms, and preferably between about 20 and 24 carbon atoms. The length, degree of saturation, and whether the fatty acid is naturally occurring in the brain affects the ability of the fatty acid to serve as a carrier to deliver the 20 agent across the blood brain barrier to an active site in the brain. Fatty acids which are partially unsaturated and occur naturally in the brain are particularly preferred as carriers. Fatty acids which occur naturally in the brain include those 25 with 16 carbon atoms and 0, 1 or 2 double bonds. It has been found that C18:3 is superior in its ability to deliver a compound across the blood brain barrier, and 4, 7, 10, 13, 16, 19 docosahexaenoic acid has also been found to be particularly useful in delivering agents across the blood brain barrier.

Branched chain fatty acids having between 16 and 26 carbon atoms can also be used in the present invention. A 30 hydrogen atom of the foregoing fatty acids can be replaced with a methyl, ethyl or isopropyl substituent at various positions along the carbon chains.

Other carrier include the naturally occurring polyisoprenoids (dolicols) and analogs thereof.

The active agent can be coupled to the fatty acid via a 35 group capable of being attached directly or indirectly to the hydroxyl group of the fatty acid. The hydroxyl group of the

fatty acid can form, for example, an ester of amide bond with the agent. A hydroxyl group or amino group of the active agent can form a bond with the fatty acid. A variety of reactions can be used involving reacting the agent or a
5 protected derivative thereof with the corresponding fatty acid carrier or an activated derivative thereof. A free hydroxyl group can form an ester bond with the fatty acid or activated derivative thereof, and the free amino group can form an amide bond with the fatty acid or activated derivative thereof.

10 The targeting and prodrug strategies described above can be combined to produce a compound that can be transported as a prodrug to a desired site of action and then unmasked to reveal an active compound.

15 In another embodiment of the present invention, the active agent is contained within a compatible biodegradable polymer in the form of microspheres. As used herein the term "microspheres" includes microcapsules, nanocapsules, and nanospheres.

20 Microcapsules and microspheres are conventionally free flowing powders consisting of spherical particles of 2 millimeters or less in diameter, usually 500 microns or less in diameter. Particles less than 1 micron are conventionally referred to as nanocapsules or nanospheres. For the most part, the difference between a microcapsule and a nanocapsule,
25 or a microsphere and a nanosphere, is size. Generally, there is little, if any, difference between the internal structure of the two.

30 The microcapsule or nanocapsule has its encapsulated agent centrally located within a membrane. This membrane may be termed a wall-forming polymeric material. Because of their internal structure, permeable microcapsules designed for controlled-release applications release their agent at a constant rate (called a "zero order" rate of release).

35 In addition, the microspheres may encompass "monolithic" and similar particles in which the active agent is dispersed throughout the particle. That is, the internal structure is a matrix of the bioactive agent and a polymer excipient.

Examples of suitable excipients include lactose, sucrose, mannitol, sorbitol, cellulose preparations, calcium phosphates, binders, such as starch paste from maize starch, wheat starch, rice starch, potato starch, gelatin, tragacanth, 5 methyl cellulose, hydropropylmethylecellulose, sodium carboxymethylcellulose and/or polyvinyl pyrrolidone. If desired, disintegrating agents may be added, such as the above-mentioned starches, as well as carboxymethyl starch, cross-linked polyvinyl pyrrolidone, agar, alginic acid, sodium 10 alginate, and the like.

Auxiliaries include flow-regulating agents and lubricants, such as silica, talc, stearic acid or salts thereof and/or polyethylene glycol. Dragee cores are provided with suitable coatings which, if desired, are resistant to 15 gastric juices. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, polyethylene glycol and/or titanium dioxide, lacquer solutions and suitable organic solvents or solvent mixtures.

In order to produce coatings resistant to gastric juices, 20 solutions of suitable cellulose preparations, such as acetyl cellulose phthalate or hydroxypropylmethyl cellulose phthalate are used. Dyestuffs or pigments may be added to the tablets or dragee coatings, for example, for identification or in 25 order to characterize different combinations of active compound doses.

Other pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such 30 as glycerol or sorbitol. The push-fit capsules can contain the active compounds in the form of granules which may be mixed with filler, such as lactose, binder, such as starches, and/or lubricants, such as talc or magnesium stearate and, 35 optionally, stabilizers. In soft capsules, the active compounds are preferably dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added.

Possible pharmaceutical preparations which can be used rectally include, for example, suppositories, which consist of a combination of the active compounds with a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols, or higher alkanols. In addition, it is also possible to use gelatin rectal capsules which consist of a combination of the active compounds with a base. Possible base materials include, for example, liquid triglycerides, polyethylene glycols, or paraffin hydrocarbons.

Suitable formulations for parenteral administration include aqueous suspensions of the active ingredients, as well as appropriate oily injection suspensions. Suitable lipophilic vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol and/or dextran. Optionally, the suspension may also contain stabilizers.

The compounds of the present invention may be administered in a variety of convenient forms, orally, parenterally, rectally, or percutaneously to treat dementia. The dosage required for each patient may vary widely, depending upon the degree of dementia and the individual patient response. However, in general, a dosage of from about 0.001 to about 100 mg/kg of body weight is appropriate for most patients.

The foregoing description of the specific embodiments will so fully reveal the general nature of the invention that others can, by applying current knowledge, readily modify and/or adapt for various applications such specific embodiments without undue experimentation and without departing from the generic concept, and, therefore, such adaptations and modifications should and are intended to be comprehended within the meaning and range of equivalents of the disclosed embodiments. It is to be understood that the

phraseology or terminology employed herein is for the purpose of description and not of limitation. The means, materials, and steps for carrying out various disclosed functions may take a variety of alternative forms without departing from the invention. Thus the expressions "means to..." and "means for...", or any method step language, as may be found in the specification above and/or in the claims below, followed by a functional statement, are intended to define and cover whatever structural, physical, chemical or electrical element or structure, or whatever method step, which may now or in the future exist which carries out the recited function, whether or not precisely equivalent to the embodiment or embodiments disclosed in the specification above, i.e., other means or steps for carrying out the same function can be used; and it is intended that such expressions be given their broadest interpretation.

All references cited herein, including journal articles or abstracts, published or unpublished U.S. or foreign patent applications, issued U.S. or foreign patents, or any other references are entirely incorporated by reference herein, including all data, tables, figures, and text present in the cited references. Additionally, the entire contents of the references cited within the references cited herein are also incorporated by reference in their entirety.

References to known method steps, conventional method steps, known methods or conventional methods is not in any way an admission that any aspect, description, or embodiment of the present invention is disclosed, taught, or suggested in the relevant art.

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15-03-2001

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CLMS

WHAT IS CLAIMED IS:

1. A method for improving mental performance in patients having symptoms of reduced mental performance and are neither in a state of non-insulin dependent diabetes nor a state of general impaired glucose tolerance, comprising administering to such a patient an effective amount of an agent which improves insulin sensitivity in the brain.
2. The method according to claim 1, wherein the agent is one which increases glucose utilization in discrete brain areas.
3. The method according to claim 2, wherein the discrete areas are selected from the group consisting of blood brain barrier microvessels and areas in the brain associated with mental performance or memory.
4. The method according to claim 1, wherein the agent is one which improves glucose utilization in astrocytes or glial cells.
5. A method according to claim 1, wherein the agent is selected from the group consisting of insulin sensitizers.
6. The method according to claim 5, wherein the agent is a thiazolidinedione.
7. The method according to claim 6, wherein the thiazolidinedione is selected from the group consisting of troglitazone, rosiglitazone, pioglitazone, darglitazone and englitazone.

8. The method according to claim 5, wherein the agent is an oxyzolidinedione.

9. The method according to claim 8, wherein the agent is JTT 501.

10. The method according to claim 1, wherein the agent activates the PPAR gamma receptor.

11. The method according to claim 1, wherein the agent has agonist or partial agonist activity at the PPAR gamma receptor.

12. The method according to claim 11 wherein the agent is a substituted 4-hydroxy-phenylalcanoic acid derivative.

13. The method according to claim 11, wherein the agent is a non-thiazolidinedione, non-oxyzolidinedione.

14. The method according to claim 13 wherein the agent is GL 262570.

15. The method according to claim 1, wherein the agent selectively activates one of the sub-types of the human PPAR gamma receptor.

16. The method according to claim 1, wherein the agent activates a RxR receptor that forms a heterodimer with a PPAR gamma receptor.

17. The method according to claim 1, wherein the agent is a combination of a PPAR gamma activator and an RxR receptor activator.

18. The method according to claim 1, wherein the agent is a natural product or is derived from a natural product.

19. The method according to claim 1, wherein the agent interacts with a PPAR alpha receptor or a PPAR delta receptor.

20. The method according to claim 1, wherein the agent interacts with the insulin transduction process so that the net effect is to increase the sensitivity or responsiveness of the insulin signal.

21. The method according to claim 1, wherein the agent is administered in conjunction with at least one agent to improve mental performance.

22. The method according to claim 21, wherein the agent to improve mental performance is selected from the group consisting of carnitine, acetyl-carnitine and cerebral enhancers.

23. A method according to claim 1, wherein the patient is one with Alzheimer's Disease.

24. The method according to claim 1, wherein the agent is delivered in the form of a prodrug.

25. The method according to claim 24, wherein the agent is provided in the form of an acid addition salt.

26. The method according to claim 24, wherein agent is linked through a spacer to a dihydropyridine redox moiety.

27. The method according to claim 1, wherein the agent is delivered in a form that enables the agent to cross the blood brain barrier.

28. The method according to claim 27, wherein the agent is delivered in conjunction with an effective amount of egrressin to enable delivery of the agent across the blood brain barrier.

29. The method according to claim 27, wherein the agent is formulated as a non-ionic compound.

30. The method according to claim 27, wherein the agent is delivered microencapsulated in a poly(lactide-co-glycolide) biodegradable polymer.

ABSTRACT

Brain glucose utilization can be increased by administering an agent that improves central nervous system insulin sensitivity. By improving the central nervous system insulin sensitivity and increasing brain glucose utilization, age-related memory loss and dementia can be prevented and/or reduced. The improvement in brain glucose utilization is independent of treatment for Type II diabetes. Among the central nervous system insulin sensitizers that can be administered to increase brain glucose utilization are thiazolidinediones, including troglitazone and pioglitazone. Other useful compounds include oxazolidinediones, including JPP501, and non-chiral acyclic agents, including GL 262370, and substituted 4-hydroxy-phenylalcanoic acid derivatives which are PPAR gamma receptor activators. All of these agents act on the nuclear receptor Ppar gamma. In a preferred embodiment, the agents are administered in the form of prodrugs which are designed to cross the blood brain barrier.

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Page 1 of 2 Pages Original Substitute Supplemental Atty. Docket: CHAIN=4A

Combined Declaration for Patent Application and Power of Attorney

As a below-named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name; and that I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

INCREASING BRAIN GLUCOSE UTILIZATION

the specification of which (check one)

- is attached hereto;
- was filed in the United States under 35 U.S.C. §111 on _____, as U.S. Appln. No. _____ *; or
- was/will be filed in the U.S. under 35 U.S.C. §371 by entry into the U.S. national stage of an international (PCT) application, PCT/US99/30066; filed December 17, 1999, entry requested on June 18, 2001 *; national stage application received U.S. Appln. No. _____ *; §371/§102(e) date _____ * (* if known)

and was amended on June 18, 2001 (if applicable).

(include dates of amendments under PCT Art. 19 and 34 if PCT)

I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above; and I acknowledge the duty to disclose to the Patent and Trademark Office (PTO) all information known by me to be material to patentability as defined in 37 C.F.R. §1.56.

I hereby claim foreign priority benefits under 35 U.S.C. §§ 119 (a)-(d) and 365 (b) of any prior foreign application(s) for patent, inventor's or plant breeder's rights certificate(s), or under §365(a) of any PCT application which designated at least one country other than the U.S., listed below:

Application No.	Country	Filing Date (MM/DD/YYYY)
_____	_____	_____

If I claimed foreign priority above, I hereby identify below any foreign application for patent (including an international (PCT) application designating a country other than the United States) or for an inventor's or plant breeder's certificate, having a filing date before that of the earliest application from which foreign priority is claimed (if left blank, then there are none):

Non-Priority Application No.	Country	Filing Date (MM/DD/YYYY)
_____	_____	_____

I hereby claim the benefit under 35 U.S.C. §119(e) of any United States provisional applications listed below:

Application No.	Filing Date (MM/DD/YYYY)
60/112,669	12/17/1998
60/122,258	02/24/1999

I hereby claim the benefit under 35 U.S.C. §120 of any prior U.S. non-provisional application(s) or under §365(c) of any prior PCT international application(s) designating the U.S., listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in such U.S. or PCT international application in the manner provided by the first paragraph of 35 U.S.C. §112, I acknowledge the duty to disclose to the PTO all information which is material to patentability as defined in 37 C.F.R. §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

Application No.	Filing Date (MM/DD/YYYY)	Status (patented, pending, abandoned)
_____	_____	_____

As a named inventor, I hereby appoint the following registered practitioners to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

All of the practitioners associated with Customer Number 001444

Direct all correspondence to the address associated with Customer Number 001444, which is presently:

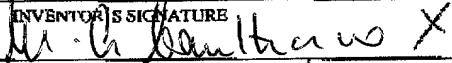
BROWDY AND NEIMARK, P.L.L.C.
624 Ninth Street, N.W.
Washington, D.C. 20001-5303
(202) 628-5197

Page 2 of 2 Pages

Title: INCREASING BRAIN GLUCOSE UTILIZATIONU.S. Application filed _____, Serial No. _____
PCT Application filed _____, Serial No. _____

The undersigned hereby authorizes the U.S. Attorneys or Agents appointed herein to accept and follow instructions from _____ as to any action to be taken in the U.S. Patent and Trademark Office regarding this application without direct communication between the U.S. Attorneys or Agents and the undersigned. In the event of a change of the persons from whom instructions may be taken, the U.S. Attorneys or Agents appointed herein will be so notified by the undersigned.

I hereby further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. §1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

FULL NAME OF FIRST INVENTOR Daniel G. CHAIN	INVENTOR'S SIGNATURE 	DATE 23.09.01
RESIDENCE Jerusalem, Israel <input checked="" type="checkbox"/>	CITIZENSHIP Israel	
POST OFFICE ADDRESS 1 Beit Eshel Street, Old Katamon, 93227 Jerusalem, Israel		
FULL NAME OF SECOND JOINT INVENTOR Mike CAWTHORNE	INVENTOR'S SIGNATURE 	DATE 20.09.01
RESIDENCE Buckingham, Great Britain <input checked="" type="checkbox"/>	CITIZENSHIP Great Britain	
POST OFFICE ADDRESS The University of Buckingham, Buckingham MK 18 1EG, Great Britain		
FULL NAME OF THIRD JOINT INVENTOR	INVENTOR'S SIGNATURE	DATE
RESIDENCE	CITIZENSHIP	
POST OFFICE ADDRESS		
FULL NAME OF FOURTH JOINT INVENTOR	INVENTOR'S SIGNATURE	DATE
RESIDENCE	CITIZENSHIP	
POST OFFICE ADDRESS		
FULL NAME OF FIFTH JOINT INVENTOR	INVENTOR'S SIGNATURE	DATE
RESIDENCE	CITIZENSHIP	
POST OFFICE ADDRESS		
FULL NAME OF SIXTH JOINT INVENTOR	INVENTOR'S SIGNATURE	DATE
RESIDENCE	CITIZENSHIP	
POST OFFICE ADDRESS		

ALL INVENTORS MUST REVIEW APPLICATION AND DECLARATION BEFORE SIGNING. ALL ALTERATIONS MUST BE INITIALED AND DATED BY ALL INVENTORS PRIOR TO EXECUTION.
NO ALTERATIONS CAN BE MADE AFTER THE DECLARATION IS SIGNED. ALL PAGES OF DECLARATION MUST BE SEEN BY ALL INVENTORS.